Regulation of PCDH15 function in mechanosensory hair cells by alternative splicing of the cytoplasmic domain.

Journal: Development

Publication Year: 2011

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PubMed link: 21427143

Public Summary:

Scientific Abstract:
Protocadherin 15 (PCDH15) is expressed in hair cells of the inner ear and in photoreceptors of the retina. Mutations in PCDH15 cause Usher Syndrome (deaf-blindness) and recessive deafness. In developing hair cells, PCDH15 localizes to extracellular linkages that connect the stereocilia and kinocilium into a bundle and regulate its morphogenesis. In mature hair cells, PCDH15 is a component of tip links, which gate mechanotransduction channels. PCDH15 is expressed in several isoforms differing in their cytoplasmic domains, suggesting that alternative splicing regulates PCDH15 function in hair cells. To test this model, we generated three mouse lines, each of which lacks one out of three prominent PCDH15 isoforms (CD1, CD2 and CD3). Surprisingly, mice lacking PCDH15-CD1 and PCDH15-CD3 form normal hair bundles and tip links and maintain hearing function. Tip links are also present in mice lacking PCDH15-CD2. However, PCDH15-CD2-deficient mice are deaf, lack kinociliary links and have abnormally polarized hair bundles. Planar cell polarity (PCP) proteins are distributed normally in the sensory epithelia of the mutants, suggesting that PCDH15-CD2 acts downstream of PCP components to control polarity. Despite the absence of kinociliary links, vestibular function is surprisingly intact in the PCDH15-CD2 mutants. Our findings reveal an essential role for PCDH15-CD2 in the formation of kinociliary links and hair bundle polarization, and show that several PCDH15 isoforms can function redundantly at tip links.